



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :  C07K 14/47, C12N 15/12, 15/63		A1	(11) International Publication Number: WO 00/68265  (43) International Publication Date: 16 November 2000 (16.11.00)
(21) International Application Number: PCT/US00/12842  (22) International Filing Date: 10 May 2000 (10.05.00)		(74) Agents: CADENA, Deborah, L. et al.; Campbell & Flores LLP, 7th floor, 4370 La Jolla Village Drive, San Diego, CA 92122 (US).	
(30) Priority Data: 09/309,487 10 May 1999 (10.05.99) US		(81) Designated States: AE, AG, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), DM, DZ, EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR (Utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 09/309,487 (CIP) Filed on 10 May 1999 (10.05.99)		Published With international search report.	
(71) Applicant (for all designated States except US): THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US/US]; 12th floor, 1111 Franklin Street, Oakland, CA 94607-5200 (US).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): SELSTED, Michael, E. [US/US]; 16 Young Court, Irvine, CA 92612 (US). TANG, Yi-Quan [CN/US]; 22 Schubert Court, Irvine, CA 92612 (US). YUAN, Jun [CN/US]; 34 Club Vista, Dove Canyon, CA 92679 (US). OUELLETTE, Andre, J. [US/US]; 32 Harvey Court, Irvine, CA 92612 (US).			
(54) Title: ANTIMICROBIAL THETA DEFENSINS AND METHODS OF USING SAME			
(57) Abstract			
<p>The present invention relates to an isolated cyclic peptide, theta defensin, having antimicrobial activity, and to theta defensin analogs. A theta defensin can have the amino acid sequence Xaa1-Xaa2-Xaa3-Xaa4-Xaa5-Xaa1-Xaa6-Xaa4-Xaa4-Xaa1-Xaa1-Xaa6-Xaa4-Xaa5-Xaa1-Xaa3-Xaa7-Xaa8, wherein Xaa1 to Xaa8 are defined; wherein Xaa1 can be linked through a peptide bond to Xaa8; and wherein crosslinks can be formed between Xaa3 and Xaa3, between Xaa5 and Xaa5, and between Xaa7 and Xaa7. For example, the invention provides a theta defensin having the amino acid sequence Gly-Phe-Cys-Arg-Cys-Leu-Cys-Arg-Arg-Gly-Val-Cys-Arg-Cys-Ile-Cys-Thr-Arg (SEQ ID NO:1), wherein the Gly at position 1 (Gly-1) is linked through a peptide bond to Arg-18, and wherein disulfide bonds are present between Cys-3 and Cys-16, between Cys-5 and Cys-14, and between Cys-7 and Cys-12. The invention also provides nucleic acids encoding theta defensins and antibodies that specifically bind a theta defensin. In addition, the invention relates to methods of using theta defensin to reduce or inhibit microbial growth or survival.</p>			
EXHIBIT A			

## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION  
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
 US Department of Commerce  
 United States Patent and Trademark  
 Office, PCT  
 2011 South Clark Place Room  
 CP2/5C24  
 Arlington, VA 22202  
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 10 January 2001 (10.01.01)	International application No. PCT/US00/12842	Applicant's or agent's file reference FP-UC 4131
International filing date (day/month/year) 10 May 2000 (10.05.00)	Priority date (day/month/year) 10 May 1999 (10.05.99)	
Applicant SELSTED, Michael, E. et al		

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

06 December 2000 (06.12.00)

in a notice effecting later election filed with the International Bureau on:

\_\_\_\_\_

2. The election  was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer Jean-Marc Vivet  Telephone No.: (41-22) 338.83.38
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## PATENT COOPERATION TREATY

PCT

**NOTIFICATION CONCERNING  
SUBMISSION OR TRANSMITTAL  
OF PRIORITY DOCUMENT**

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

CADENA, Deborah, L.  
Campbell & Flores LLP  
7th floor  
4370 La Jolla Village Drive  
San Diego, CA 92122  
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) <b>31 July 2001 (31.07.01)</b>			
Applicant's or agent's file reference <b>FP-UC 4131</b>	<b>IMPORTANT NOTIFICATION</b>		
International application No. <b>PCT/US00/12842</b>	International filing date (day/month/year) <b>10 May 2000 (10.05.00)</b>		
International publication date (day/month/year) <b>16 November 2000 (16.11.00)</b>	Priority date (day/month/year) <b>10 May 1999 (10.05.99)</b>		
Applicant <b>THE REGENTS OF THE UNIVERSITY OF CALIFORNIA et al</b>			

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(\*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
10 May 1999 (10.05.99)	09/309,487	US	03 July 2001 (03.07.01)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No. (41-22) 740.14.35	Authorized officer  S. Mandallaz  Telephone No. (41-22) 338.83.38
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WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



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(54) Title: ANTIMICROBIAL THETA DEFENSINS AND METHODS OF USING SAME

(57) Abstract

The present invention relates to an isolated cyclic peptide, theta defensin, having antimicrobial activity, and to theta defensin analogs. A theta defensin can have the amino acid sequence Xaa1-Xaa2-Xaa3-Xaa4-Xaa5-Xaa1-Xaa6-Xaa4-Xaa4-Xaa1-Xaa1-Xaa6-Xaa4-Xaa5-Xaa1-Xaa3-Xaa7-Xaa8, wherein Xaa1 to Xaa8 are defined; wherein Xaa1 can be linked through a peptide bond to Xaa8; and wherein crosslinks can be formed between Xaa3 and Xaa3, between Xaa5 and Xaa5, and between Xaa7 and Xaa7. For example, the invention provides a theta defensin having the amino acid sequence Gly-Phe-Cys-Arg-Cys-Leu-Cys-Arg-Arg-Gly-Val-Cys-Arg-Cys-Ile-Cys-Thr-Arg (SEQ ID NO:1), wherein the Gly at position 1 (Gly-1) is linked through a peptide bond to Arg-18, and wherein disulfide bonds are present between Cys-3 and Cys-16, between Cys-5 and Cys-14, and between Cys-7 and Cys-12. The invention also provides nucleic acids encoding theta defensins and antibodies that specifically bind a theta defensin. In addition, the invention relates to methods of using theta defensin to reduce or inhibit microbial growth or survival.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/12842

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 C07K14/47 C12N15/12 C12N15/63

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, STRAND, CHEM ABS Data, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TANG, YI-QUAN ET AL: "A cyclic antimicrobial peptide produced in primate leukocytes by the ligation of two truncated alpha.-defensins" SCIENCE (WASHINGTON, D. C.) (1999), 286(5439), 498-502 , 1999, XP000919300 Figs. 2-3 ---	2-32, 34-38, 40-49, 51-83
P, X	TAM, JAMES P. ET AL: "Marked increase in membranolytic selectivity of novel cyclic tachyplesins constrained with an antiparallel two-beta. strand cystine knot framework" BIOCHEM. BIOPHYS. RES. COMMUN. (2000), 267(3), 783-790 , 2000, XP000917243 Figures ---	2-32, 34-38, 40-49, 51-83

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&amp;\* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

7 August 2000

24.08.00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
Fax: (+31-70) 340-3016

Authorized officer

Kronester-Frei, A

## INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/US 00/12842

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 11663 A (BOUGUERET LYDIE ; CHUMAKOV ILYA (FR); GENSET (FR)) 11 March 1999 (1999-03-11)  CLAIMS, EXAMPLES ---	2-32, 34-38, 40-49, 51-83
A	WO 99 13080 A (ZYMOGENETICS INC) 18 March 1999 (1999-03-18)  claims, examples ---	2-32, 34-38, 40-49, 51-83
A	WO 96 16075 A (UNIV CALIFORNIA ; SHRINER S HOSPITAL FOR CRIPPLE (US)) 30 May 1996 (1996-05-30)  claims -----	2-32, 34-38, 40-49, 51-83

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 00/12842

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 83 because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2.  Claims Nos.: 1,33,39,50 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark : Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 83 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box I.1

Claims Nos.: 83

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Continuation of Box I.2

Claims Nos.: 1,33,39,50

Present claims 1, 33, 39, 50 (functional fragment thereof) and dependent subject-matter relate to an extremely large number of possible peptides/pharmaceutical compositions/nucleic acids/vectors. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the peptides/pharmaceutical compositions/nucleic acids/vectors claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the peptides/pharmaceutical compositions/nucleic acids/vectors being prepared in the examples and closely related homologous compounds etc./those compounds etc. mentioned in the description at pages 12, lines 14 to pages 17, lines 16.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/US 00/12842

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9911663	A 11-03-1999	FR	2767832 A	05-03-1999
		AU	9079898 A	22-03-1999
		EP	1009767 A	21-06-2000
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WO 9913080	A 18-03-1999	AU	9391598 A	29-03-1999
		EP	1012285 A	28-06-2000
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WO 9616075	A 30-05-1996	US	5844072 A	01-12-1998
		AU	697378 B	01-10-1998
		AU	3958795 A	17-06-1996
		EP	0792279 A	03-09-1997
		JP	10509047 T	08-09-1998
		US	6057425 A	02-05-2000
		US	5840498 A	24-11-1998
		US	5731149 A	24-03-1998
		ZA	9508887 A	09-05-1996
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## PATENT COOPERATION TREA

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>FP-UC 4131</b>	<b>FOR FURTHER ACTION</b>	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. <b>PCT/US 00/ 12842</b>	International filing date (day/month/year) <b>10/05/2000</b>	(Earliest) Priority Date (day/month/year) <b>10/05/1999</b>

Applicant

THE REGENRTS OF THE UNIVERSITY OF CALIFORNIA

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
    - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
  - b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :
    - contained in the international application in written form.
    - filed together with the international application in computer readable form.
    - furnished subsequently to this Authority in written form.
    - furnished subsequently to this Authority in computer readable form.
    - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
    - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished
2.  Certain claims were found unsearchable (See Box I).
3.  Unity of invention is lacking (see Box II).
4. With regard to the title,
  - the text is approved as submitted by the applicant.
  - the text has been established by this Authority to read as follows:
5. With regard to the abstract,
  - the text is approved as submitted by the applicant.
  - the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is Figure No.
  - as suggested by the applicant.
  - because the applicant failed to suggest a figure.
  - because this figure better characterizes the invention.

None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 00/12842

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 83  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see FURTHER INFORMATION sheet PCT/ISA/210**
  
2.  Claims Nos.: 1, 33, 39, 50  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
**see FURTHER INFORMATION sheet PCT/ISA/210**
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
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### Remark on Protest

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/12842

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 C07K14/47 C12N15/12 C12N15/63

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, STRAND, CHEM ABS Data, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TANG, YI-QUAN ET AL: "A cyclic antimicrobial peptide produced in primate leukocytes by the ligation of two truncated alpha.-defensins" SCIENCE (WASHINGTON, D. C.) (1999), 286(5439), 498-502 , 1999, XP000919300 Figs. 2-3 ---	2-32, 34-38, 40-49, 51-83
P, X	TAM, JAMES P. ET AL: "Marked increase in membranolytic selectivity of novel cyclic tachyplesins constrained with an antiparallel two.-beta. strand cystine knot framework" BIOCHEM. BIOPHYS. RES. COMMUN. (2000), 267(3), 783-790 , 2000, XP000917243 Figures ---	2-32, 34-38, 40-49, 51-83
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/12842

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 11663 A (BOUGUELERET LYDIE ;CHUMAKOV ILYA (FR); GENSET (FR)) 11 March 1999 (1999-03-11)  CLAIMS, EXAMPLES ---	2-32, 34-38, 40-49, 51-83
A	WO 99 13080 A (ZYMOGENETICS INC) 18 March 1999 (1999-03-18)  claims, examples ---	2-32, 34-38, 40-49, 51-83
A	WO 96 16075 A (UNIV CALIFORNIA ;SHRINER S HOSPITAL FOR CRIPPLE (US)) 30 May 1996 (1996-05-30)  claims -----	2-32, 34-38, 40-49, 51-83

**INTERNATIONAL SEARCH REPORT**

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